Accepted Manuscript

Electrochemical regioselective azidoiodination of alkenes

Wei-qing Yan, Meng-ying Lin, R. Daniel Little, Cheng-Chu Zeng

PII: S0040-4020(16)31355-2

DOI: 10.1016/j.tet.2016.12.058

Reference: TET 28350

To appear in: *Tetrahedron*

Received Date: 24 October 2016

Revised Date: 20 December 2016

Accepted Date: 23 December 2016

Please cite this article as: Yan W-q, Lin M-y, Little RD, Zeng C-C, Electrochemical regioselective azidoiodination of alkenes, *Tetrahedron* (2017), doi: 10.1016/j.tet.2016.12.058.

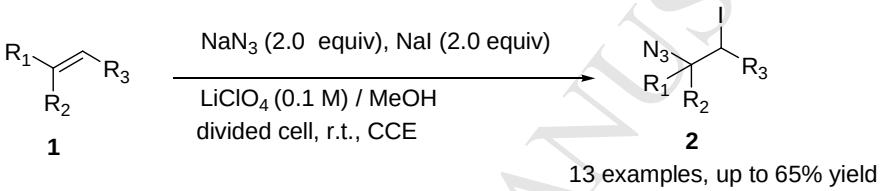
Electrochemical regioselective azidoiodination of alkenes

Wei-qing Yan,[a] Meng-ying Lin,[a] R. Daniel Little [b] and Cheng-Chu Zeng,[a*]

[a] *College of Life Science & Bioengineering, Beijing University of Technology, Beijing 100124, China. Corresponding author: zengcc@bjut.edu.cn*

[b] *Department of Chemistry & Biochemistry, University of California, Santa Barbara, Santa Barbara, California 93106-9510, USA*

Graphical Abstract:



Abstract

An efficient electrochemical approach to the vicinal iodoazides has been developed through constant current electrolysis of alkenes with NaN_3 and NaI in methanol. The reaction is proposed to proceed via a cyclic iodonium intermediate and thereby gives Markovnikov addition products exclusively.

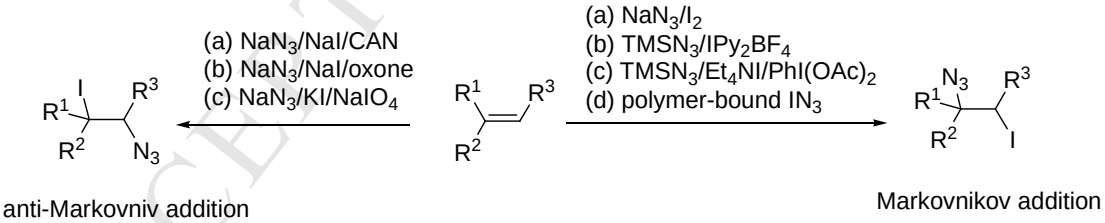
Key words: azidoiodination of alkenes; Electrosynthesis; Markovnikov addition; cyclic iodonium intermediate

Introduction

Difunctionalization of alkenes constitutes one of the most important chemical transformations in organic chemistry.[1-3] Among them, azidoiodination of alkenes has attracted considerable attention since the resulting vicinal iodoazides contain extraordinarily useful iodo and azido functional groups, which can readily be transformed into versatile intermediates such as vinyl azides, amines, aziridine and tetrazoles.[4-7] In addition, along with the development of "click chemistry", various organic azides are required as starting materials for producing 1,2,3-triazoles possessing a wide spectrum of biological activities.[8] Consequently, the development

of an efficient and regioselective protocol to produce vicinal iodoazides is a worthy objective.

Vicinal iodoazides are generally synthesized by reactions of alkenes with IN_3.[9-11] Because of the explosive character, IN_3 is conventionally generated in situ by using different combinations of azido and iodide sources in the presence of an oxidant. Notably, depending on the reaction conditions and the reagent combinations used, the in situ generated IN_3 may undergo homolytic or heterolytic cleavage, which can lead to anti-Markovnikov addition (radical pathway) or Markovnikov addition (via a cyclic iodonium ion mechanism) products in reactions with asymmetric alkenes, respectively. For example, using CAN as an oxidant, reaction with NaN_3 and NaI gave exclusively anti-Markovnikov addition product.[12] Such are also the cases using combinations of NaN_3/NaI/oxone and NaN_3/KI/$NaIO_4$ (Scheme 1).[13,14] In contrast, Markovnikov addition reaction occurs when employing combinations of NaN_3/I_2, $TMSN_3/IPy_2BF_4$, $TMSN_3/Et_4NI/PhI(OAc)_2$ and polymer-bound IN_3 (Scheme 1).[15-18] While much progress has been made, these methods suffer from certain drawbacks such as usage of “expensive” reagents and a large excess of oxidant. Consequently, a mild and practical method that involves less toxic reagents and minimizes waste is of importance.



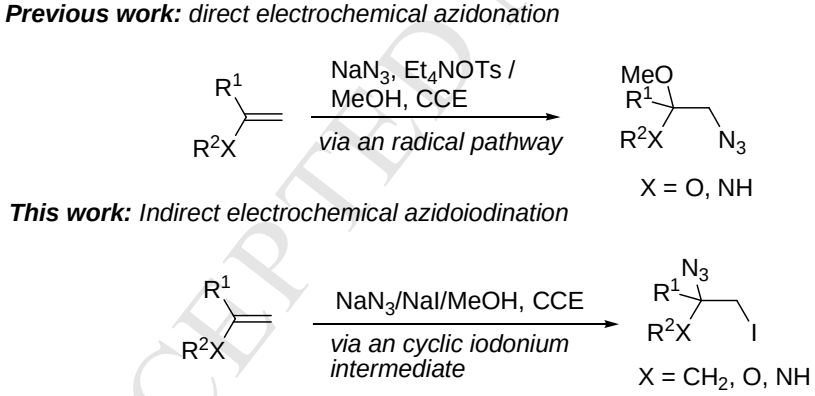
Scheme 1. Azidoiodination of alkenes under different conditions

Toward this end, we describe herein our efforts to apply electrochemistry to achieve oxidative azidoiodination of alkenes. To the best of our knowledge, there is only one report of the electrochemical introduction of the azido unit onto an alkene double bond. Thus, the anodic oxidation of enol ethers and enamide in methanol containing 0.17 M of Et_4NOTs as supporting electrolyte in the presence of NaN_3 brought about azidomethoxylation and gave the corresponding acetal and

N,O-acetal.[19] Notably, in this electrochemical azidomethoxylation, the addition of an azido group was observed to take place regioselectively at the β-position of the enol ether or enamide *via a radical mechanism* (Scheme 2).

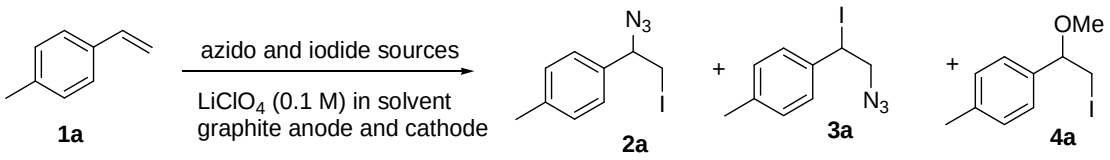
As a continuation of our ongoing program involving halide-mediated electrochemical synthesis, we hypothesized that the electrochemical oxidation of iodide ion ought to form molecular iodine, which may in situ undergo reaction with NaN_3 to afford IN_3. Thereafter an azidoiodination reaction with an alkene ought to provide the corresponding iodoazides.

Herein, we report an efficient electrochemical method for the regioselective synthesis of vicinal iodoazides. In the protocol, IN_3 is generated electrochemically in situ, avoiding the utilization of external oxidants or corrosive molecular iodine and is therefore environmentally benign. In addition, quite different from the electrochemical azidomethoxylation referred to above, our protocol proceeds via a cyclic iodonium mechanism to afford Markovnikov addition products exclusively (Scheme 2).



Scheme 2. Electrochemical azidoiodination of alkenes

Results and Discussion



Scheme 3. Conditional optimization of azidoiodination of *p*-methylstyrene **1a**

We commenced our studies by using *p*-methylstyrene (**1a**) as model substrate and a combination of NaN_3/NaI as the IN_3 precursor (Scheme 3 and Table 1). Constant current electrolyses were performed at 15 mA/cm^2 in an H-type cell using two graphite plates as the working electrode and cathode. Given the fact that the ratio of the IN_3 precursor to the alkene and the nature of solvent influence the azidoiodination reaction of alkenes, the ratio of styrene and NaN_3/NaI was initially investigated. When 1 mmol of **1a**, 1.2 equiv of NaN_3 and 1.2 equiv of NaI was used, the Markovnikov addition-type adduct **2a** was obtained exclusively, albeit in but a 34% yield (Table 1, entry 1). Based on the extensive work of Hassner and coworkers,[9-11] the formation of this Markovnikov addition-type adduct indicates that the electrochemical azidoiodination of alkenes may involves the heterolytic cleavage of IN_3 to iodonium (I^+) and azido anion (N_3^-). Increasing of the ratio resulted in a dramatic improvement of yield to 63% and 73% when the azido and iodide source increased to 1.5 equiv and 2 equiv of styrene (Table 1, entries 2 and 3). A further increase to 3 equiv of NaN_3/NaI did not improve the yield (Table 1, entry 4). Therefore, 2 equiv of NaN_3/NaI to one equiv of styrene was the ratio of choice.

Solvent screening demonstrated that MeOH played a crucial role for the Markovnikov addition-type azidoiodination reaction. The presence of water in methanol turned out to give a slightly lower yield (65% vs 73%; Table 1, entry 5). When MeCN was used as a solvent, an anti-Markovnikov regioisomer **3a** was also isolated in 18% yield, along with the desired adduct **2a** (22% yield) (Table 1, entry 6). We assume that the formation of anti-Markovnikov iodoazides involves a radical pathway and that the electrochemically generated IN_3 in CH_3CN may undergo both homolytic and heterolytic cleavage. In the case of CF_3CH_2OH, due to the low solubility of NaN_3, most of the starting styrene was recovered (Table 1, entry 7).

Next, the combination of NaN_3 and different iodide sources were evaluated for the azidoiodination reaction. It was observed that all of the iodide salts tested proceed

smoothly, albeit in a slightly lower yields than that with NaI (Table 1, entries 3 and 8-11). For example, when KI was used, adduct **2a** was obtained in 50% yield; it changed to 66%, 55% and 61% when the iodide sources were NH_4I, Et_4NI and *n*-Bu_4NI, respectively. Interestingly, when $TMSN_3$, instead of NaN_3, was used as the azido source, 1-(2-iodo-1-methoxyethyl)-4-methylbenzene, **4a**, was isolated exclusively in 35% yield (entry 12). The formation of **4a** may result from the nucleophilic attack of methoxide (generated from cathodic reduction of methanol) to the cyclic iodonium. Finally, it was observed that room temperature was preferable for the azidoiodination reaction since the yields of **2a** decreased to 55% when the reaction was performed at 0 ^oC and to 27% when carried out at 60 ^oC (entries 13-14).

Based on the results described above, we conclude that the optimal reaction conditions call for using NaI and NaN_3 as the IN_3 precursor and a 2:1 ratio of NaN_3/NaI to alkene. The reaction is best performed in a divided cell using methanol as the solvent.

Table 1. Optimization of the model reaction.

Entry	Substrate to reagent ratio (**1a:** I^-: N_3^-)	Solvent	I-source	Temperature (^oC)	Yield of 2a (%) [b]
1	1:1.2:1.2	MeOH	NaI	25	34
2	1:1.5:1.5	MeOH	NaI	25	63
3	1:2:2	MeOH	NaI	25	73
4	1:3:3	MeOH	NaI	25	70
5	1:2:2	MeOH + H_2O (v: v= 5: 1)	NaI	25	65
6	1:2:2	MeCN	NaI	25	22 [c]
7	1:2:2	CF_3CH_2OH	NaI	25	0

8	1:2:2	MeOH	KI	25	50
9	1:2:2	MeOH	NH_4I	25	66
10	1:2:2	MeOH	Et_4NI	25	55
11	1:2:2	MeOH	*n*-Bu_4NI	25	61
12	1:2:2	MeOH	NaI	25	-[d]
13	1:2:2	MeOH	NaI	0	55
14	1:2:2	MeOH	NaI	60	27

[a] Reaction conditions: **1a** (1.0 mmol), NaN_3 and NaI in 12 mL of solvent, divided cell, current density of 15 mA/cm^2, graphite plate anode and cathode, $LiClO_4$ (0.1 M) was added as a conducting salt.

[b] ^{1}H NMR yield, using trimethoxybenzene as the internal standard.

[c] Along with 18% yield of **3a**

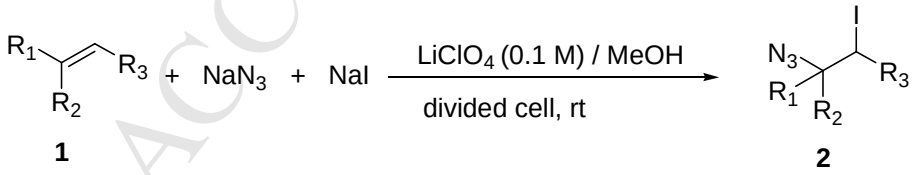
[d] Me_3SiN_3 was used as the azido source and **4a** was isolated in 35% yield.

With the optimized reaction conditions in hand, we then examined the scope and limitations of the azidoiodination reaction using these conditions. As shown in Table 2, azidoiodination of styrene derivatives **1b-h** proceeded smoothly and the corresponding adducts **2b-h** were obtained. It was observed that substrates containing electron rich substituents lead to significantly higher yields than those bearing electron withdrawing groups. For example, when *p*-methoxystyrene was subjected to the reaction conditions, adduct **2c** was obtained in 55%. However, the electron deficient fluoro-substituted styrene **1d** gave very low yield of **2d** (20%) under exactly conditions. In addition, *para*-substituted adducts afford a higher yield than its *ortho*-substituted counterpart (note **2e** and **2g** with yields of 40% vs. 10%). In the case of 2-phenylpropene **1h**, adduct **2h** was obtained in 44% yield. For the unactivated terminal alkene **1i**, the desired **2i** was isolated in a 47% yield.

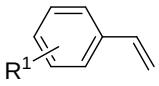
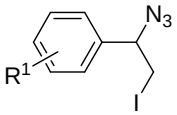
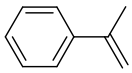
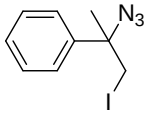
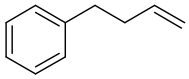
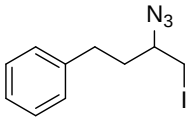
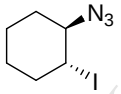
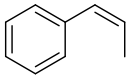
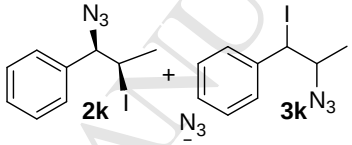
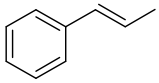
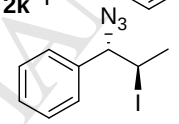
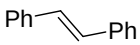
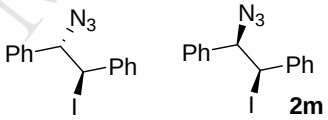
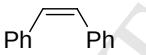
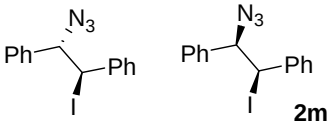
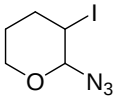
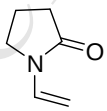
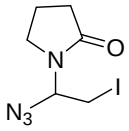
Internal alkenes were also investigated. Cyclohexene gave a 30% yield of *trans*-addition product **2j**. When *cis*-phenyl-1-propene **1k** was subjected to

electrochemical azidoiodination with NaN_3/NaI under the standard conditions, a mixture of regioisomers, the Markovnikov product **2k** and anti-Markovnikov product **3k**, were obtained in a 40% combined yield. Strangely, when *trans*-phenyl-1-propene **1l** was used as a substrate, the adduct **2l** was not detected, whereas the starting **1l** disappeared. In the case of *cis*-stilbene, a 1:1.2 diastereomeric mixture of 1-azido-2-iodo-1,2-diphenylethane, **2m** was isolated in a combined 50% yield. The same diastereomeric ratio resulted when *trans*-stilbene was exposed to electrolysis in the presence of NaN_3 and NaI and 55% yield of diastereomers **2m** was obtained. The literature reports that *trans*- and *cis*-stilbene afford *erythro*- and *threo*-**2m**, respectively, under conventional chemical conditions. [20] That *anti*-selectivity was not observed under our conditions using *trans*- and *cis*-stilbene, suggests that the expected intermediate cyclic iodonium is not stable and that ring opening occurs to give an intermediate carbon cation, thereby leading to partial *syn*-addition. When alkenes containing a heteroatom appended directly to the alkene group were subjected to electrolysis under the standard conditions (using methanol alone as solvent), the reaction also occurred, but with lower yield. For example, when tetrahydropyran **1o** and 1-vinylpyrrolidin-2-one **1p** were used, adducts **2o** and **2p** were isolated in 17% and 25% yields, respectively.

Table 2. Scope of alkene using methanol as solvent [a]



1 **2**

Entry	Alkenes **1**	Products **2**	Yield (%)[b]
1	 **1a**: R^1 = *p*-Me	 **2a**: R^1 = *p*-Me	65
2	**1b**: R^1 = H	**2b**: R^1 = H	55
3	**1c**: R^1 = *p*-OMe	**2c**: R^1 = *p*-OMe	55
4	**1d**: R^1 = *p*-F	**2d**: R^1 = *p*-F	20
5	**1e**: R^1 = *p*-Cl	**2e**: R^1 = *p*-Cl	40
6	**1f**: R^1 = *p*-Br	**2f**: R^1 = *p*-Br	40
7	**1g**: R^1 = *o*-Cl	**2g**: R^1 = *o*-Cl	10
8	 **1h**	 **2h**	44
9	 **1i**	 **2i**	47
10	 **1j**	 **2i**	30
11	 **1k**	 **2k** + **3k**	40, **2k**:**3k** = 1:1
12	 **1l**	 **2l**	trace
13	 **1m**	 **2m**	50, dr: 1: 1.2
14	 **1n**	 **2m**	55, dr: 1:1.2
15	 **1o**	 **2o**	17
16	 **1p**	 **2p**	25

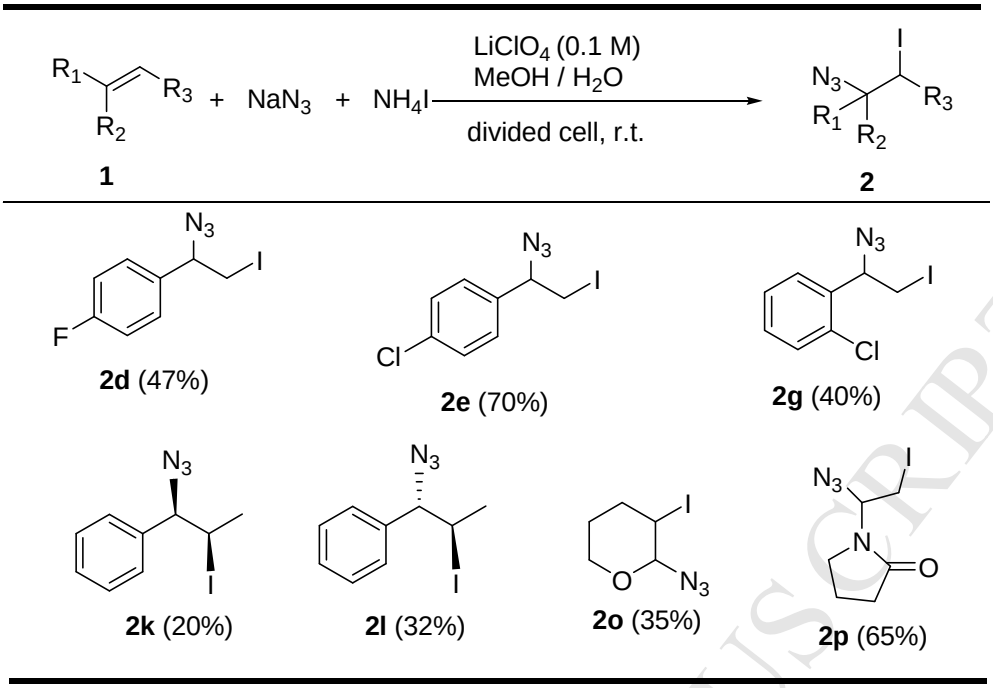
[a] Reaction conditions: alkene **1** (1.0 mmol), NaN_3 (2.0 mmol) and NaI (2.0 mmol) in 12 mL of methanol, divided cell, current density of 15 mA/cm^2, graphite plate anode and cathode, $LiClO_4$ (0.1 M) was added as a conducting salt.

[b] Isolated yield after column chromatograph

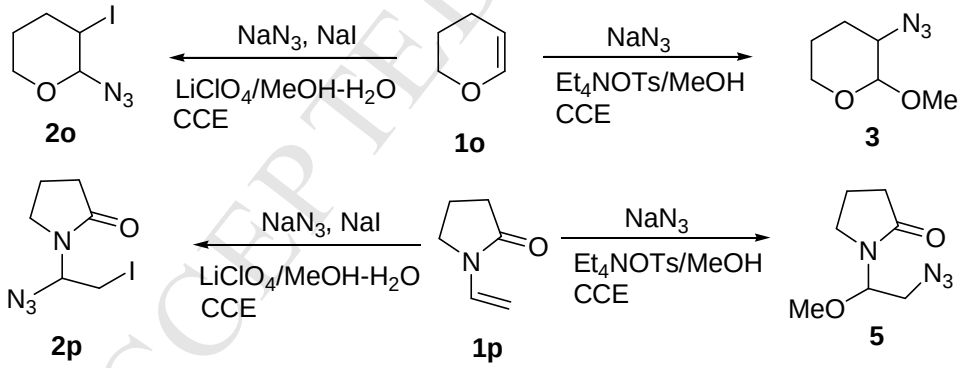
Due to the lower yields for some of the substrates (such as **1d** and **1g**), further

optimization was carried out. We found that an improved yield of **2** was obtained when a mixture of methanol and water (*v:v* = 5:1) was employed as the solvent under otherwise identical electrolytic conditions. For example, **2d, 2e** and **2g** were isolated in 47%, 70% and 40% yields, respectively, much higher than that obtained when using methanol alone as the solvent. Interestingly, under the modified conditions, (*z*)-1-propenylbenzene **1k** only gave the Markovnikov *trans*-addition product **2k** in a yield of 20%, and **1l** afforded the desired adduct **2l** in a yield of 32% (Table 3). Although the exact reason for the regioselective reaction of **1k** in MeOH/H_2O is not clear at the presence, we assume that the polarity of the solvent may play an important role, higher polarity of a mixed solution benefits heterolytic cleavage of IN_3 and leads to Markovnikov addition product, **2k**. This observation can be demonstrated by the azidoiodination reactions of **1a** in CH_3CN and MeOH. In the former, both **2a** and **3a** were isolated simultaneously, whereas only **2a** was produced in MeOH (see entries 3 and 6 in Table 1). Under the modified conditions, improved yields of **2o** and **2p** were also obtained. It is worth mentioning that our results differ from those reported by Nishiguchi et al.[19] Thus, the direct electrochemical oxidation of **1o** and **1p** in methanol using Et_4NOTs as a conducting salt afforded 3-azido-2-ethoxy-tetrahydro-2H-pyran (**3**) and 1-(2-azido-1-methoxyethyl)pyrrolidin-2-one (**5**) wherein the azido group was introduced into the β-position (Scheme 4).

Table 3. Scope of alkene using aqueous methanol as solvent [a]



[a] Reaction conditions: alkene **1** (1.0 mmol), NaN_3 (1.5 mmol) and NH_4I (1.5 mmol) in 12 mL of mixed solvent of methanol and water (*v*:*v* = 5:1), divided cell, current density of 15 mA/cm^2, graphite plate anode and cathode, $LiClO_4$ (0.1 M) was added as a conducting salt.

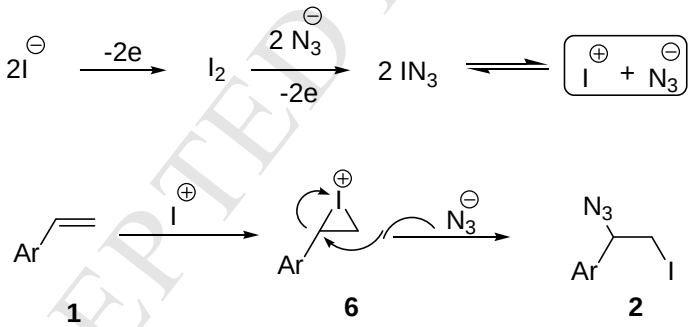


Scheme 4. Regioselectivity

To gain insight into the mechanism of the electrochemical azidoiodination of alkenes, we performed cyclic voltammetry experiments involving the alkenes and the IN_3 precursors. It was found that the oxidation peak potentials of NaI and NaN_3 were 0.45 V and 0.85 V (vs $Ag/AgNO_3$ in 3 M KCl), which indicates that NaI is

electrochemically much easier to oxidize than NaN_3. That no oxidation peak was observed for styrene **1a** up to the oxidation potential of the solvent methanol clearly demonstrates that styrene ought not to be oxidized under the standard conditions.

In addition, for the conventional chemical azidoiodination of alkenes, it has been demonstrated that radical pathway gives anti-Markovnikov addition products, while Markovnikov addition proceeds via a cyclic iodonium intermediate. Based on our cyclic voltammetry measurements and literature reports, we propose a mechanism shown in Scheme 5 for the electrochemical synthesis of vicinal iodoazides. As illustrated, the reaction begins with the anodic oxidation of iodide to generate molecular iodine, which reacts with azido ion to produce IN_3. When using polar solvents such as methanol and water, the in situ generated IN_3 reacts predominantly as a source of I^+ to form cyclic iodonium intermediate **6** whose capture by azide at the more substituted carbon affords the Markovnikov type addition product **2**.



Scheme 5. Plausible mechanism for the regioselective azidoiodination of alkenes

Conclusion

In summary, a new and efficient electrochemical method for the synthesis of vicinal iodoazides has been developed. The procedure uses a constant current electrolysis of NaN_3 and NaI in the presence of alkenes in an H-type cell employing methanol as the solvent. A wide range of substrates proved to be compatible with the protocol, delivering the products in a Markovnikov fashion. The results suggest that the reaction proceeds via a cyclic iodonium intermediate. Further application of these

ideas and results to other types of reactions is underway in our laboratory.

4. Experimental

4.1 Instruments and reagents

NMR spectra were recorded using a 400 MHz spectrometer (400 MHz ^{1}H frequency, 100 MHz ^{13}C frequency). Chemical shifts are given as δ values (internal standard: TMS). Coupling constants are reported in Hz. Starting materials and solvents were obtained from commercial sources and used without further purification. Products were purified by chromatography on silica gel (petroleum ether/EtOAc).

4.2 Typical procedure for the electrochemical synthesis of 2

An H-type cell with a G4-fritted glass as a diaphragm was equipped with a carbon anode (2.0 × 1 cm^2) and a carbon cathode (2.0 × 1 cm^2) and connected to a DC regulated power supply. To the anodic compartment was added alkene (1 mmol), NaN_3 (2 mmol), iodide salt (2 mmol) and 12 mL of methanol dissolved in 0.1 M $LiClO_4$, whereas the cathodic compartment was added only 12 mL 0.1 M $LiClO_4$. The mixture was electrolyzed using constant current conditions (~15 mA/cm^2) at room temperature under magnetic stirring. When TLC analysis indicated that the electrolysis was complete (witnessed by the disappearance of the amide), the solvent was removed under reduced pressure. The residue was poured into a saturated aqueous solution of $Na_2S_2O_3$ and the product was then extracted with DCM (3×20 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using a mixture of petroleum ether/EtOAc (v : v = 150 : 1) as eluent to afford the desired pure product.

1-(1-Azido-2-iodoethyl)-4-methylbenzene (2a) [15]

Yield: 186 mg, 65%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 3.40 (d, J = 7.2 Hz, 2H), 4.71 (t, J = 6.8 Hz, 1H), 7.21-7.26 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.4, 21.3, 67.0, 126.6, 129.8, 134.9, 139.1.

1-(1-Azido-2-iodoethyl)benzene (2b) [15]

Yield: 150 mg, 55%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.42 (d, J = 6.8 Hz, 2H), 4.75 (t, J = 7.2 Hz, 1H), 7.34-7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.4, 67.2, 126.8, 129.1, 129.1, 138.0.

1-(1-Azido-2-iodoethyl)-4-methoxybenzene (2c) [21]

Yield: 167 mg, 55%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38-3.40 (m, 2H), 3.84 (s, 3H), 4.70 (t, J = 6.8 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.5, 55.4, 66.7, 114.4, 128.0, 129.9, 160.03.

1-(1-Azido-2-iodoethyl)-4-fluorobenzene (2d)

Yield: 137 mg, 47%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38-3.40 (m, 2H), 4.73 (t, J = 7.2 Hz, 1H), 7.10-7.15 (m, 2H), 7.31-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.1, 66.3, 116.0, 116.2, 128.5, 128.6; IR (KBr) (cm^{-1}): υ 2106, 1698, 1588, 1487, 1072, 1010,; HRMS (ESI) *m/z* calcd for C_8H_7FI $(M\text{-}N_3)^+$: 248.9576, found: 248.9574.

1-(1-Azido-2-iodoethyl)-4-chlorobenzene (2e) [21]

Yield: 222 mg, 70%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38 (d, J = 6.4 Hz, 2H), 4.72 (t, J = 6.8 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.0, 66.3, 128.1, 129.3, 134.9, 136.4.

1-(1-Azido-2-iodoethyl)-4-bromobenzene (2f)

Yield: 137 mg, 39%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38 (d, J = 7.2 Hz, 2H), 4.71 (t, J = 6.8 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.9, 66.3, 123.1, 128.4, 132.3, 136.9; IR (KBr) (cm^{-1}): υ 2106, 1603, 1510, 1230; HRMS (ESI): *m/z* calcd for C_8H_7BrI $(M\text{-}N_3)^+$: 308.8776, found: 308.8769.

1-(1-Azido-2-iodoethyl)-2-chlorobenzene (2g)

Yield: 123 mg, 40%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.33 (dd, J = 10.4 Hz, J = 8.8 Hz, 1H), 3.52 (dd, J = 10.4 Hz, J = 4.4 Hz, 1H), 5.24 (dd, J = 8.4 Hz, J = 4.0 Hz, 1H), 7.32-7.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.2, 63.3, 127.6, 127.6, 130.0, 130.1, 132.7, 135.9; IR (KBr) (cm^{-1}): υ 2109, 1473, 1443; HRMS (ESI) m/z calcd for C_8H_9ClIN $(M\text{-}N_2\text{+}H)^+$: 279.9389, found: 279.9379.

(2-Azido-1-iodopropan-2-yl)-benzene (2h)

Yield: 127 mg, 44%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (s, 3H), 3.49 (d, J = 10.8 Hz, 1H), 3.53 (d, J = 10.4 Hz, 1H), 7.35-7.47 (m, 5H); ^{13}C R (100 MHz, $CDCl_3$): δ 17.7, 25.2, 65.1, 125.7, 128.3, 128.8, 140.8; IR (KBr) (cm^{-1}): υ 2980, 2105, 1494, 1446; HRMS (ESI): *m/z* calcd for $C_9H_{10}I$ $(M\text{-}N_3)^+$: 244.9827, found: 244.9826.

(3-Azido-4-iodobutyl)-benzene (2i)

Yield: 142 mg, 47%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.86-2.10 (m, 2H), 2.69-2.87 (m, 2H), 3.31 (d, J = 6.0 Hz, 2H), 3.40-3.44 (m, 1H), 7.23-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.3, 32.0, 36.2, 61.8, 126.4, 128.4, 128.7, 140.4; IR (KBr) (cm^{-1}): υ 3026, 2924, 2857, 2106, 1602, 1496, 1453; HRMS (ESI) *m/z*: calcd for $C_{10}H_{13}IN$ $(M+H\text{-}N_2)^+$: 274.0093, found: 274.0084.

1-Azido-2-iodocyclohexane (2j) [15]

Yield: 77 mg, 30%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32-1.60 (m, 4H), 1.87-2.48 (m, 4H), 3.50-3.55 (m, 1H), 3.94-4.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ .23.9, 27.1, 32.0, 33.4, 38.5, 67.2.

***Cis*-(1-Azido-2-iodopropyl)-benzene (2k)**

Yield: 57 mg, 20%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78 (d, J = 7.2 Hz, 3H), 4.42 (quint, J = 6.8 Hz, 1H), 4.52 (d, J = 8.0 Hz, 1H), 7.32-7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7, 30.2, 73.6, 127.3, 128.9, 129.0, 136.9; IR (KBr) (cm^{-1}): υ2102, 1493, 1453, 763, 700; HRMS (ESI): *m/z* calcd for $C_9H_{10}I$ $(M\text{-}N_3)^+$: 244.9827, found: 244.9825.

***Trans*-(1-Azido-2-iodopropyl)-benzene (2l)** [22]

Yield: 93 mg, 32%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90 (d, J = 6.8 Hz, 3H), 4.37 (quint, J = 6.4 Hz, 1H), 4.80 (d, J = 6.0 Hz, 1H), 7.35-7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5, 29.0, 72.7, 127.4, 128.9, 128.9, 137.4.

(1-Azido-2-iodoethane-1,2-diyl)-dibenzene (2m,2n) d.r. =1:1.2 [16]

Yield: 197 mg, 65%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.98 (d, J = 9.6 Hz, 1H), 5.15 (d, J = 9.2 Hz, 1H), 5.22 (d, J = 9.6 Hz, 1H), 5.26 (d, J = 9.2 Hz, 1H), 7.15-7.50 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.4, 36. 8, 71.9. 72.8, 127.3, 127.7, 128.3, 128.5, 128.6, 128.7, 128.8, 129.1, 136.3. 137.7, 140.1, 140.2; IR (KBr) (cm^{-1}): υ 3031, 2103, 756.9, 698.

2-Azido-3-iodo-tetrahydro-*2H*-pyran (2o) [15]

Yield: 87 mg, 35%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67-1.73 (m, 2H), 2.04-2.13 (m, 1H), 2.38-2.45 (m, 1H), 3.67-3.73 (m, 1H), 3.92-3.97 (m, 1H), 4.11-4.16 (m, 1H), 4.96 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.4, 27.4, 34.0, 66.2, 92.4.

1-(1-Azido-2-iodoethyl)pyrrolidin-2-one (2p)

Yield: 180 mg, 65%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.07-2.14 (m, 2H), 2.46 (t, J = 8.0 Hz, 2H), 3.17 (t, J = 8.8 Hz, 1H), 3.31-3.45 (m, 3H), 5.82-5.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.0, 18.1, 30.7, 41.3, 68.2, 175.8; IR (KBr) (cm^{-1}): υ 2958, 2108, 1697, 1413; HRMS (ESI): *m/z* calcd for C_6H_9INO $(M\text{-}N_3)^+$ 237.9729, found: 237.9729.

1-(1-Azido-2-iodoethyl)-4-methylbenzene (2a) and 1-(2- Azido-1-iodoethyl)-4-methylbenzene (3a) [12]

Yield: 114.8 mg, 40%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.53 (s, 3H), 2.39 (s, 7H), 3.40 (d, J = 6.8 Hz, 4.2H), 3.95 (d, J = 8.0 Hz, 2H), 4.71 (t, J = 6.8 Hz, 2.1H), 5.172 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 8 Hz, 2H), 7.24 (m, 9H), 7.34 (d, J = 8 Hz, 2H).

1-(2-Iodo-1-methoxyethyl)-4-methylbenzene (4a) [23]

Yield: 96 mg, 35%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 3.33 (s, 3H), 3.32-3.38 (m, 2H), 4.30-4.33 (m, 1H), 7.21-7.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.9, 21.4, 57.3, 83.4, 126.5, 129.5, 136.8, 138.3.

(1-azido-2-iodopropyl)-benzene (2k) and (2-azido-1-iodopropyl)-benzene (3k) [22]

Yield: 114 mg, 40%, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (d, J = 6.4 Hz, 4H), 1.54 (d, J = 6.4 Hz, 3H), 1.78 (d, J = 6.8 Hz, 6H), 3.81-3.88 (m, 1H), 3.94-4.01 (m ,1H), 4.24-4.31 (m, 2H), 4.52 (d, J = 8.4 Hz, 2H), 4.96 (d, J = 8 Hz, 1H), 5.01 (d, J = 8 Hz, 1H), 7.29-7.36 (m, 11H), 7.38-7.43 (m, 12H)**.**

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (No. 21272021, 21472011) and the national key research and development program (2016YFD0400801)

References

1. Zeng, X.-M. *Chem. Rev*. **2013**, *113*, 6864.
2. McDonald, R. I.; Liu, G.-S.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981.
3. Shimizu, Y.; Kanai, M. *Tetrahedron Lett*. **2014**, *55*, 3727.
4. Hassner, A.; Fowler, F. W. *J. Org. Chem*., **1968**, *33*, 2686.
5. Wasserman, H. H.; Brunner, R. K.; Buynak, J. D.; Carter, C. G.; Oku, T.; Robinson, R. P. *J. Am. Chem. Soc*. **1985**, *107*, 519.
6. Van Ende, D.; Krief, A. *Angew. Chem.* **1974**, *86*, 311.
7. Yoneyama, H.; Usami, Y.; Komeda, S.; Harusawa, S. *Synthesis.* **2013**, *45*, 1051.
8. Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. *Med. Res. Rev*. **2008**, *28*, 278.
9. Hantzsch, A. *Ber, Dtsch, Chem. Ges*. **1900**, *33*, 522.
10. Hassner, A.; Levy, L. A. *J. Am. Chem. Soc*. **1965**, *87*, 4203.
11. Hassner, A. *Acc. Chem. Res*. **1971**, *4*, 9.
12. Nair, V.; George, T. G.; Sheeba, V.; Augustine, A.; Balagopal, L.; Nair, L. G. *Synlett.* **2000**, 1597.
13. Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. *Tetrahedron Lett*. **2002**, *43*, 1201.
14. Chouthaiwale, P. V.; Karabal, P. U.; Suryavanshi, G.; Sudalai, A. *Synthesis*, **2010**,

3879.

15. Terent'ev, A. O.; Krylov, I. B.; Kokorekin, V. A.; Nikishin, G. I. *Synth. Commun*. **2008**, *38*, 3797.
16. Barluenga, J.; Alvarez-Perez, M.; Fananas, F. J.; Gonzalez, J. M. *Adv. Synth. Catal*. **2001**, *343*, 335.
17. Kirschning, A.; Hashem, M. A.; Monenschein, H.; Rose, L.; Schoening, K. U. *J. Org. Chem*. **1999**, *64*, 6522
18. Kirschning, A.; Monenschein, H.; Schmeck, C. *Angew. Chem. Int. Ed*. **1999**, *38*, 2594.
19. Fujimoto, K.; Tokuda, Y.; Matsubara, Y.; Maekawa, H.; Mizuno, T.; Nishiguchi, I. *Tetrahedron Lett.*, **1995**, *36*, 7483.
20. Fowler, F. W.; Hassner, A. Levy, L. A. *J. Am. Chem. Soc*. **1967**, *89*, 2077.
21. Kupracz, L.; Hartwig, J.; Wegner, J.; Ceylan, S.; Kirschning, A. *Beilstein J. Org. Chem*. **2011**, *7*, 1441.
22. Zhang, X.-M.; Sarkar, S. K.; Weragoda, G. K.; Rajam, S.; Ault, B. S.; Gudmundsdottir, A. D. *J. Org. Chem*. **2014**, *79*, 653.
23. Agrawal, M, K; Adimurthy, S.; Ganguly, B.; Ghosh, P, K. *Tetrahedron*. **2009**, *65*, 2791.